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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/752,145	12/29/2000	Klim King	CPI-013CNDV4	8048

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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
ULM, JOHN D

ART UNIT	PAPER NUMBER
1646	6

DATE MAILED: 12/10/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/752,145	King et al.
Examiner	**Art Unit**
John Ulm	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1) Claims 1 to 9 are pending in the instant application. Claims 10 to 28 have been canceled as requested by Applicant in Paper Number 5, filed 29 December of 2000.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2) Claims 1 to 9 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. A relationship which is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The vast majority of G protein-coupled receptors do not interact with the vast majority of Gα subunits. The particular class of Gα subunit to which a specific receptor couples determines the type of physiological response produced by that receptor. A critical relationship of the claimed invention is that the mammalian G protein-coupled receptor employed in the claimed cell must be capable of coupling to (compatible with) the mammalian Gα subunit employed therein. If one simply chooses a mammalian G protein-coupled receptor and a mammalian Gα subunit at random, the claimed yeast cell will most likely not function as disclosed.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3) Claims 1 to 7 are rejected under 35 U.S.C. § 103 as being unpatentable over the Marullo et al. patent (5,242,822) in view of the Dietzel et al. (Cell 50:1001-1010, 25 Sep. 1987), Herskowitz et al. (Cell 50:995-996, 25 Sept. 1987) and Whiteway et al. (Cell 56:467-477, 10 Feb. 1989) publications. The Marullo et al. patent generally teaches the construction of an expression vector encoding a G protein-coupled receptor, a unicellular host containing that vector and a receptor ligand binding assay employing that unicellular host. The text in lines 24 to 31 of column 2 discloses that such hosts make it "easy" to characterize such receptors. The text beginning on line 54 of column 1 of this patent expressly identified β-adrenergic receptors as specifically suitable for this application. The text from line 20 to 38 in column 3 of this patent specifically recommends the use of *Saccharomyces cerevisiae* as a preferred host in the disclosed method as specified in the instant claims. The text in column 8 of this patent shows that the receptors described therein were useful only in ligand binding assays and no mention of signal transduction

is contained therein. The claimed invention is distinguished from Marullo et al. because it further requires a second heterologous DNA encoding a mammalian G protein α subunit.

The text in the third full paragraph on page 10012 of the Dietzel et al. publication shows that it was well known in the art that a G protein α subunit was an essential component in the transduction of a signal by a G protein-coupled receptor upon the binding of a ligand by that receptor and that the α subunit specifically interacted with the cytoplasmic domains of such receptors. The section of this publication entitled "**Complementation of *scg1* and *sst2* Mutations by the Rat α_s Subunit**" beginning on page 1005 described the recombinant DNA-mediated functional expression of a rat G protein α subunit in a yeast host cell which was incapable of expressing an endogenous G protein α subunit. This section further disclosed that the rat G protein α subunit employed therein was capable of transducing a signal from an endogenous yeast G protein-coupled receptor. Because the art of molecular biology recognized that the ability of a G protein α subunit to interact with both a ligand-activated G protein-coupled receptor and those proteins responsible for the signaling mechanism of the cell expressing that receptor protein was the critical link in the transduction of a signal by that receptor to that cell, an artisan would have presumed that the rat G protein α subunit of Dietzel et al. would transduce a signal to the recombinant yeast host cell described therein from any G protein-coupled receptor with which it could functionally interact. Because the an artisan was well aware that the only way to distinguish between receptor ligands which are agonists from those that are antagonists requires one to be able to determine if a cellular signal has been generated in a cell by that

receptor in response to the binding of a ligand , an artisan would have found it *prima facie* obvious to have expressed a mammalian G protein-coupled receptor like those which were described by Marullo et al. in a yeast host cell in conjunction with a mammalian G protein α subunit as taught by Dietzel et al. to permit the "easy" identification of agonists and antagonists of that receptor at the time that the instant invention was made. Whereas one could not be assured of the ability of that mammalian G protein-coupled receptor to transduce a signal through an endogenous yeast G protein α subunit an artisan had more than a reasonable expectation that the rat G protein α subunit would transduce this signal since it was already known to function with both mammalian G protein-coupled receptors and the signal transducing mechanisms of a yeast host cell. That artisan would have also recognized the need to employ a yeast host which did not express an endogenous G protein-coupled receptor to avoid any false signals which might by produced by that endogenous receptor.

The Herskowitz et al. publication has been relied upon because it expressly stated that "[t]he deduced amino acid sequence of the STE2 and STE3 products" [a.k.a. yeast α-factor and a-factor receptors, respectively] "revealed that they are members of the rhodopsin/β-adrenergic receptor/muscarinic acetylcholine receptor family of integral membrane proteins". This review article, in its entirety, explains why the yeast mating factor response system appears to be analogous the G protein/ G protein-coupled receptor signal transduction systems of mammals. It concludes with the statement that "[t]he apparent conservation of a sensory transduction machine from yeast to mammals provides another comforting example of the underlying unity of cell

biology". Given that yeast were known to naturally express at least two native G protein-coupled receptors, an artisan had more that a reasonable expectation that mammalian G protein-coupled receptors could be functionally expressed in a yeast host cell as taught by Marullo et al.

The Whiteway et al. publication is relied upon because it described the yeast STE4 and STE18 gene products and identified them as the yeast homologs of mammalian Gβ and γ subunits, respectively. In combination with the references cited above, this reference shows that an artisan knew that the yeast *Saccharomyces cerevisiae* naturally produced endogenous G protein-coupled receptors, a well as the yeast equivalent of the mammalian Gα, β and γ subunits which were responsible for signal transduction from those receptors, more than a year before the filing of the instant application. That artisan was also aware that a rat Gα subunit could be functionally expressed in a yeast cell lacking its endogenous Gα subunit and that the rat Gα subunit was capable of transducing a mating factor response signal from the endogenous yeast mating factor receptor to those cellular components within that yeast cell which are responsible for producing that mating factor response. Therefore, that artisan had more than a reasonable expectation that they could express a mammalian G protein-coupled receptor which was known to couple to the rat Gα subunit employed by Dietzel et al. in yeast cells functionally expressing that rat Gα subunit and that the mammalian receptor would induce a mating factor response from those cells when activated by an agonist to that mammalian receptor. That artisan would have been motivate to employ yeast in this capacity because they are genetically simpler than mammalian cells and easier to propagate and to manipulate. Further, they allow one to evaluate

the interaction of a test compound with a receptor of interest in the absence of other mammalian receptors which would inherently be present in a mammalian host cell.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Marullo et al.(U.S./ Pat. No. 5,242,822), Dietzel et al. (Cell 50:1001-1010, 25 Sep. 1987), Herskowitz et al. (Cell 50:995-996, 25 Sept. 1987) and Whiteway et al. (Cell 56:467-477, 10 Feb.. 1989) references. as applied to claims 1 to 7 above, and further in view of the Nomoto et al. publication (EMBO J. 9(3):691-696, March 1990). These claims differ from those above in further requiring the presence of a heterologous DNA sequence comprising a pheromone responsive promoter linked to an indicator gene. The Nomoto et al. publication described the construction of the yeast cell line NNY19, containing a *FUS1-lacZ* fusion gene, and disclosed the advantages of employing this cell line in the measurement of the induction of a pheromone response. To have employed a yeast cell containing a *FUS1-lacZ* fusion gene to measure the pheromone response of a yeast cell containing a mammalian G protein-coupled receptor and a compatible mammalian Gα subunit would have been *prima facie* obvious to one of ordinary skill in the art of molecular in view of this combination of references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1600